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(54) Title: NOVEL CRYSTALLINE FORMS OF LAMOTRIGINE

(57) Abstract: The present invention relates to novel crystalline forms of lamotrigine, to processes for their preparation and pharmaceutical compositions containing them.

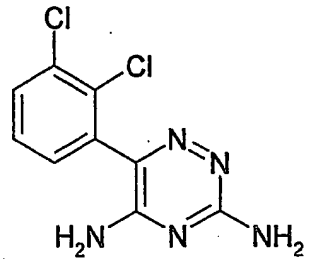
NOVEL CRYSTALLINE FORMS OF LAMOTRIGINE

FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of lamotrigine, to processes for their preparation and pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Lamotrigine of formula (1) :



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or 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine is an anti-epileptic drug and its therapeutic uses are disclosed in U.S. Pat. No. 4,602,017.

Different synthetic methods of lamotrigine are described in WO 01/049669, US 6,111,101, US 6,333,198, US 5,912,345, EP 800521, US 4,602,017.

Various polymorphic forms are disclosed in WO 02/068398.

We have discovered three novel crystalline forms of lamotrigine. The novel forms have been found to be stable over the time and does not automatically convert into other crystalline forms of lamotrigine.

The novel forms of lamotrigine is, thus, suitable for pharmaceutical preparations.

Thus the object of the present invention is to provide stable novel crystalline forms of lamotrigine, to provide a processes for preparation of the

novel crystalline forms and to provide a pharmaceutical compositions comprising these novel crystalline forms.

SUMMARY OF THE INVENTION

According to one aspect of the present invention, there is provided a novel crystalline Form I of lamotrigine characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.5, 13.9, 16.7, 18.0, 22.3, 23.6, 26.8, 27.9, 28.5, 28.9, 29.4, 31.7, 40.2, 42.3 degrees. Figure 1 shows typical Form I x-ray powder diffraction pattern.

According to another aspect of the present invention, there is provided a novel crystalline Form II of lamotrigine characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 8.9, 11.2, 12.3, 13.2, 13.9, 17.0, 17.4, 18.0, 18.2, 18.7, 19.8, 21.4, 22.1, 22.7, 25.1, 25.4, 25.7, 26.4, 26.8, 27.1, 27.5, 28.3, 28.8, 29.2, 30.1, 30.9, 31.4, 32.9, 35.3, 35.7, 36.5 degrees. Figure 2 shows typical Form II x-ray powder diffraction pattern.

According to another aspect of the present invention, there is provided a novel crystalline Form III of lamotrigine characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.9, 12.0, 13.3, 16.1, 17.0, 18.1, 18.7, 19.5, 24.4, 26.0, 26.3, 27.6, 28.1, 37.1 degrees. Figure 3 shows typical Form III x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of Form I lamotrigine comprising the steps of:

a) dissolving lamotrigine in an ester;
b) maintaining at 15°C to 30°C for about 30 minutes to 2 hours;
c) filtering Form I lamotrigine.

The ester is selected from the group consisting of ethyl acetate, methyl acetate, ethyl formate, isopropyl acetate.

According to another aspect of the present invention there is provided a process for preparation of Form II lamotrigine comprising the steps of:

a) dissolving lamotrigine in dioxane;
b) maintaining at about 15°C to about 30°C for about 1 hour to 3 hours;
c) filtering Form II lamotrigine.

According to another aspect of the present invention there is provided a process for preparation of Form III lamotrigine comprising the steps of:

a) mixing lamotrigine, isopropyl acetate, chloroform and dimethyl formamide at about 60°C to about 70°C;

b) filtering the Form III lamotrigine at about 20°C to about 30°C.

Lamotrigine prepared by any of the known methods can be used in the above processes. Lamotrigine solvate or hydrate may also be used in the above processes.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising Form I or Form II or Form III lamotrigine.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction pattern of Form I lamotrigine.

Figure 2 is a x-ray powder diffraction pattern of Form II lamotrigine.

Figure 3 is a x-ray powder diffraction pattern of Form III lamotrigine.

x-Ray powder diffraction spectrum was measured on a Siemens diffractometer.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect of the present invention, there is provided a novel crystalline Form I of lamotrigine characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.5, 13.9, 16.7, 18.0, 22.3, 23.6, 26.8, 27.9, 28.5, 28.9, 29.4, 31.7, 40.2, 42.3 degrees. Figure 1 shows typical Form I x-ray powder diffraction pattern.

According to another aspect of the present invention, there is provided a process for preparation of Form I lamotrigine. Thus lamotrigine is dissolved in an ester. The ester is selected from the group consisting of ethyl acetate, methyl acetate, ethyl formate, isopropyl acetate. The Form I lamotrigine is maintained at about 15°C to about 30°C, preferably at about 20°C to about 25°C, for about 30 minutes to about 2 hours and filtered. Lamotrigine prepared by any of the known methods can be used in the process. Lamotrigine solvate or hydrate may also be used.

According to another aspect of the present invention, there is provided a novel crystalline Form II lamotrigine characterized by an x-ray powder diffraction

pattern having peaks expressed as 2θ at about 8.9, 11.2, 12.3, 13.2, 13.9, 17.0, 17.4, 18.0, 18.2, 18.7, 19.8, 21.4, 22.1, 22.7, 25.1, 25.4, 25.7, 26.4, 26.8, 27.1, 27.5, 28.3, 28.8, 29.2, 30.1, 30.9, 31.4, 32.9, 35.3, 35.7, 36.5 degrees. Figure 2 shows typical Form II x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of Form II lamotrigine. Thus lamotrigine is dissolved in dioxane and maintained at about 15°C to about 30°C for about 1 hour to 3 hours. The separated Form II lamotrigine is filtered. Lamotrigine prepared by any of the known methods can be used in the process. Lamotrigine solvate or hydrate may also be used.

According to another aspect of the present invention, there is provided a novel crystalline Form III of lamotrigine characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.9, 12.0, 13.3, 16.1, 17.0, 18.1, 18.7, 19.5, 24.4, 26.0, 26.3, 27.6, 28.1, 37.1 degrees. Figure 3 shows typical Form III x-ray powder diffraction pattern.

According to another aspect of the present invention there is provided a process for preparation of Form III lamotrigine. Thus lamotrigine isopropyl acetate, chloroform and dimethyl formamide are mixed and heated to about 60°C to about 70°C. The contents are maintained for about 30 minutes and cooled to about 20°C to about 30°C. The Form III lamotrigine is filtered. Lamotrigine prepared by any of the known methods can be used in the process. Lamotrigine solvate or hydrate may also be used.

According to another aspect of the present invention there is provided a pharmaceutical composition comprising Form I or Form II or Form III lamotrigine. The forms of lamotrigine may be formulated in a form suitable for oral administration or injection.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope or spirit of the invention.

Example 1

Lamotrigine (10 gm) (obtained by the process described in example 1 of US 4,602,017) is mixed with ethyl acetate (100 ml) and maintained at about

70°C for 30 minutes. Then the contents are cooled to about 20°C. The solid is separated by filtration to give 9.0 gm of Form I lamotrigine.

Example 2

Lamotrigine (10 gm) (obtained by the process described in example 1 of US 4,602,017) is added to dioxane (100 ml), maintained at 50°C to 55°C for 30 minutes, cooled to 25°C and maintained at this temperature for 2 hours. The solid is separated by filtration to give 8.5 gm of Form II lamotrigine.

Example 3

Lamotrigine (10 gm) (obtained by the process described in example 1 of US 4,602,017) is added to isopropyl acetate (150 ml) and the contents are heated to about 65°C. Chloroform (50 ml) and dimethyl formamide (48 ml) are added at this temperature and stirred for 30 minutes. The contents are cooled to 25°C and filtered to give 9.5 gm of Form III lamotrigine.

Example 4

Example 1 is repeated using Form II lamotrigine instead of lamotrigine to give Form I lamotrigine.

Example 5

Example 1 is repeated using Form III lamotrigine instead of lamotrigine to give Form I lamotrigine.

Example 6

Example 2 is repeated using Form III lamotrigine instead of lamotrigine to give Form II lamotrigine.

Example 7

Example 2 is repeated using Form I lamotrigine instead of lamotrigine to give Form II lamotrigine.

Example 8

Example 3 is repeated using Form II lamotrigine instead of lamotrigine to give Form III lamotrigine.

Example 9

Example 3 is repeated using Form I lamotrigine instead of lamotrigine to give Form III lamotrigine.

We claim:

1. A crystalline lamotrigine Form I.
2. A crystalline lamotrigine, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.5, 13.9, 16.7, 18.0, 22.3, 23.6, 26.8, 27.9, 28.5, 28.9, 29.4, 31.7, 40.2, 42.3 degrees.
3. A crystalline lamotrigine, characterized by an x-ray powder diffraction pattern as in figure 1.
4. A process for preparation of Form I lamotrigine of claim 1, comprising the steps of:
   a) dissolving lamotrigine in an ester;
   b) maintaining at 15^0C to 30^0C for about 30 minutes to 2 hours;
   c) filtering Form I lamotrigine;
   wherein ester is selected from the group consisting of ethyl acetate, methyl acetate, ethyl formate, isopropyl acetate.
5. A crystalline lamotrigine Form II.
6. A crystalline lamotrigine, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 8.9, 11.2, 12.3, 13.2, 13.9, 17.0, 17.4, 18.0, 18.2, 18.7, 19.8, 21.4, 22.1, 22.7, 25.1, 25.4, 25.7, 26.4, 26.8, 27.1, 27.5, 28.3, 28.8, 29.2, 30.1, 30.9, 31.4, 32.9, 35.3, 35.7, 36.5 degrees.
7. A crystalline lamotrigine, characterized by an x-ray powder diffraction pattern as in figure 2.
8. A process for preparation of Form II lamotrigine of claim 5, comprising the steps of:
   a) dissolving lamotrigine in dioxane;
   b) maintaining at about 15^0C to about 30^0C for about 1 hour to 3 hours;
   c) filtering Form II lamotrigine.
9. A crystalline lamotrigine Form III.
10. A crystalline lamotrigine, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.9, 12.0, 13.3, 16.1, 17.0, 18.1, 18.7, 19.5, 24.4, 26.0, 26.3, 27.6, 28.1, 37.1 degrees.
11. A crystalline lamotrigine, characterized by an x-ray powder diffraction pattern as in figure 3.

12. A process for preparation of Form III lamotrigine of claim 9, comprising the steps of:

a) mixing lamotrigine, isopropyl acetate, chloroform and dimethyl formamide at about 60°C to about 70°C;

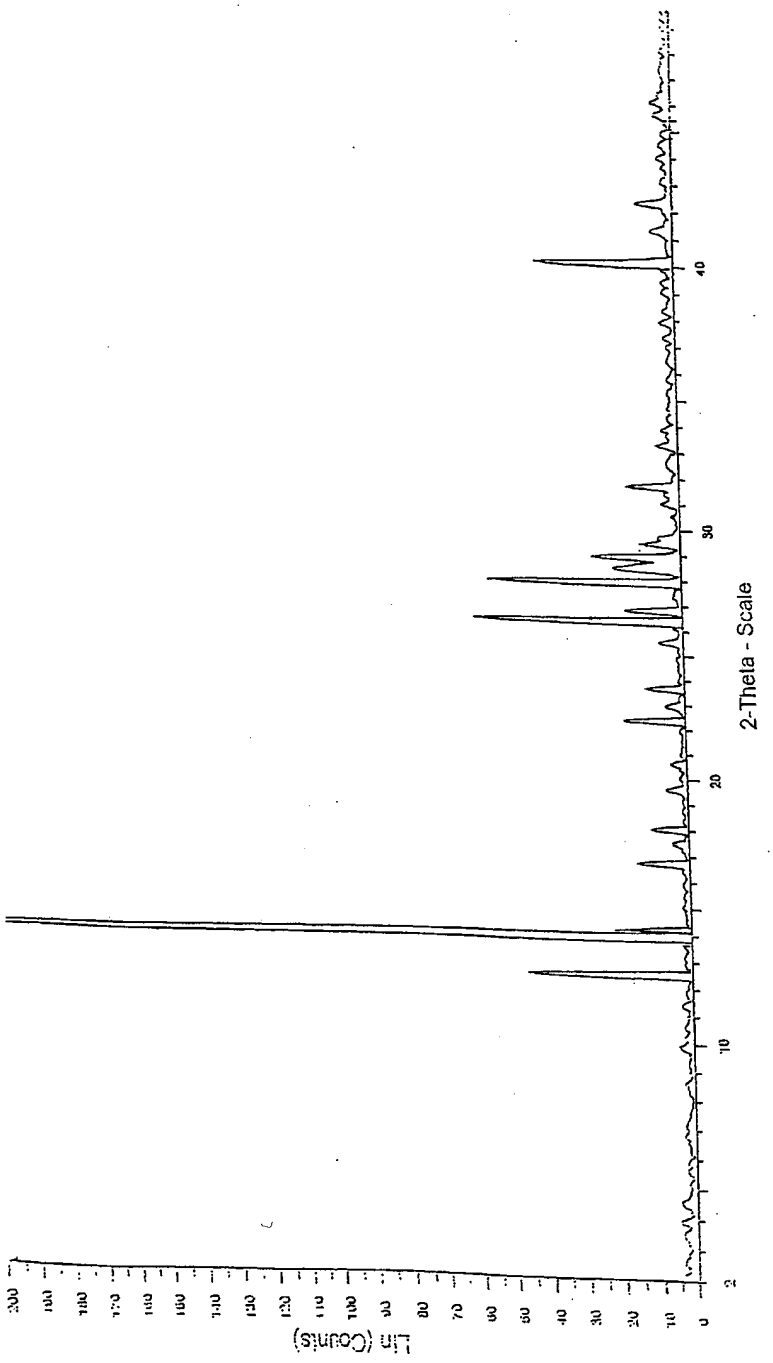
b) filtering the Form III lamotrigine at about 20°C to about 30°C.

13. A pharmaceutical composition comprising a crystalline form of lamotrigine and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition of claim 13, wherein crystalline form of lamotrigine is Form I lamotrigine of claim 1.

15. A pharmaceutical composition of claim 13, wherein crystalline form of lamotrigine is Form II lamotrigine of claim 5.

16. A pharmaceutical composition of claim 13, wherein crystalline form of lamotrigine is Form III lamotrigine of claim 9.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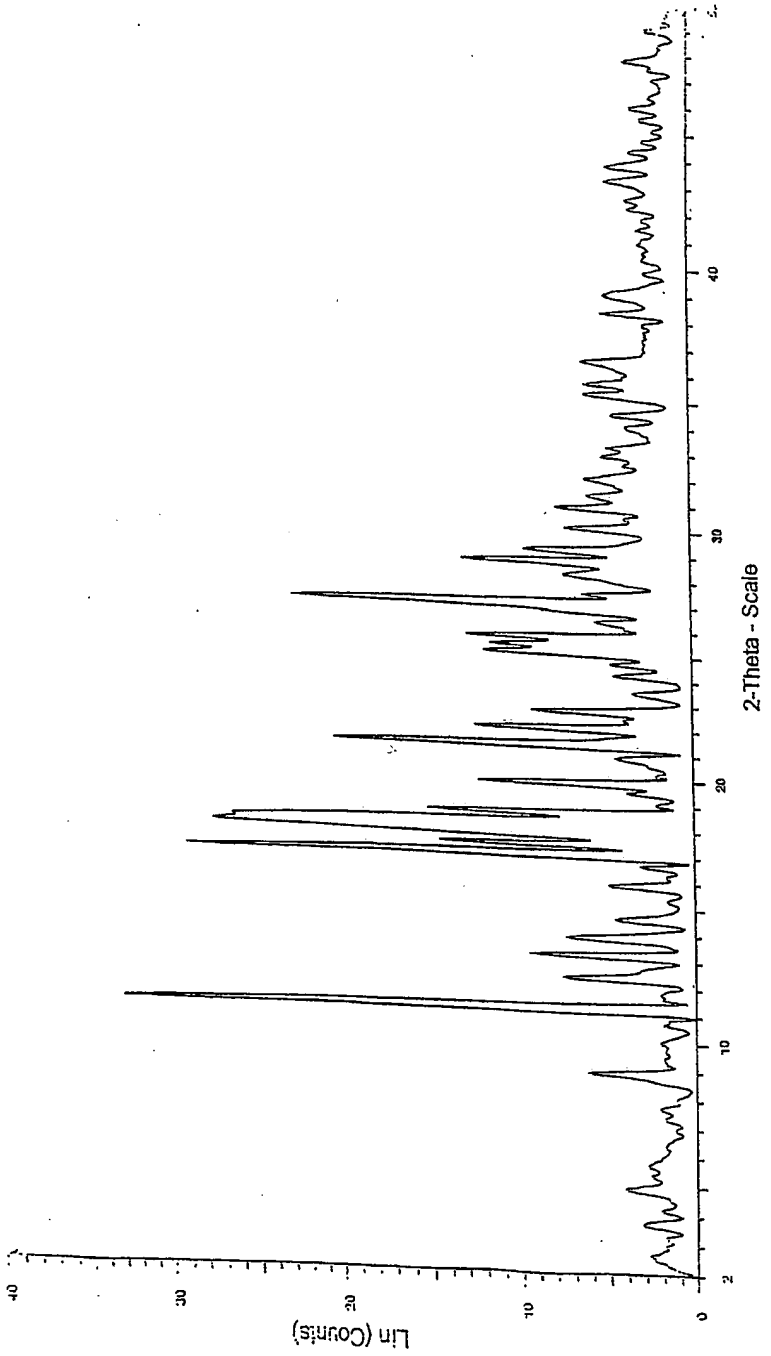
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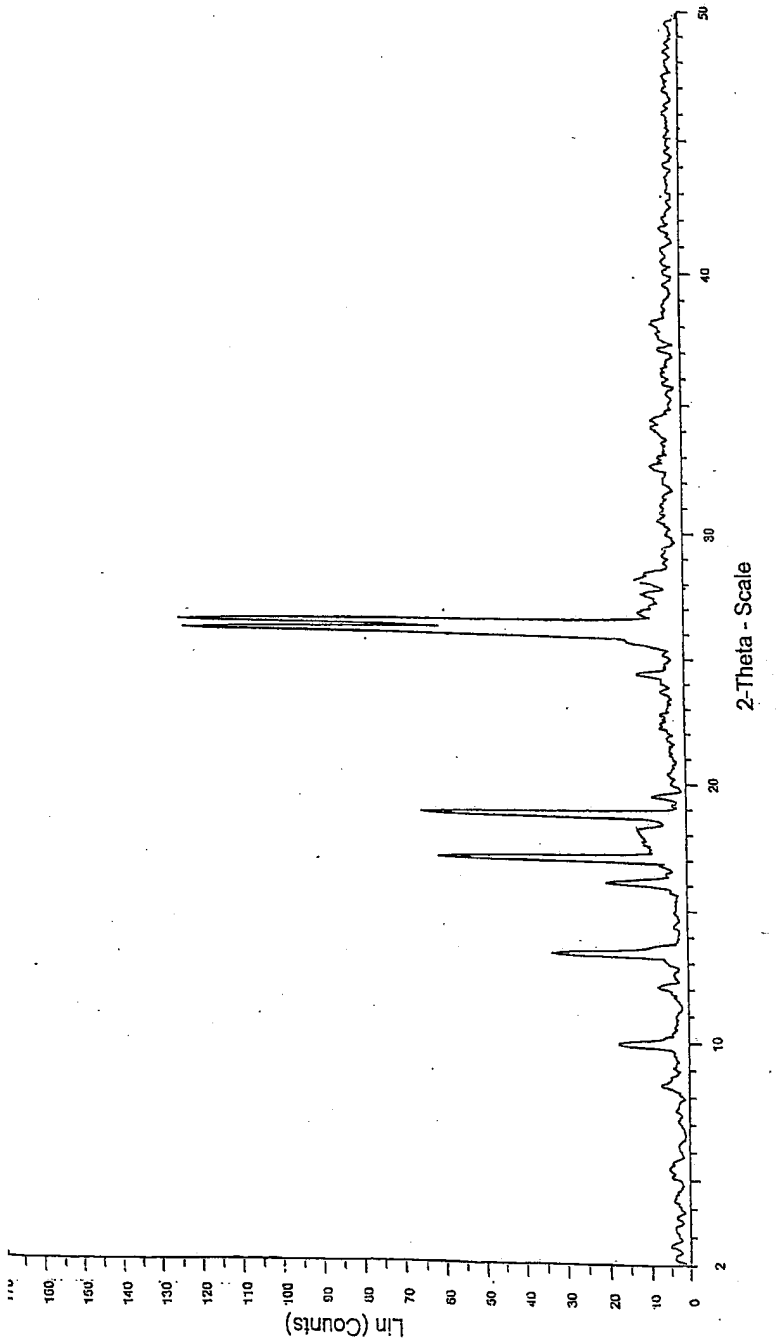
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2-Theta - Scale

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00057-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 253/075, A61K 31/53

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/068398 A1 (Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.) 6 September 2002 (06.09.02) ; cited in the application *abstract, claim 1, fig. 1-18.*	1-16
X	US 4602017 A (Baxter, Martin G.; Elphick, Albert R.; Miller, Alistair A.; Sawyer, David A.; Wellcome Foundation Ltd., UK) 22 July 1986 (22.07.86) ; cited in the application *abstract; example 1, col 6, lines 6-9.*	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2003 (12.08.2003)	11 September 2003 (11.09.2003)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer MÜLLER-HIEL R. Telephone No. 1/53424/434

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00057-0

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				MY	A	62/85	31-12-1985
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